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TUTORIAL

Development of a cortical visual neuroprosthesis for the blind: the relevance of neuroplasticity

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Abstract

Clinical applications such as artificial vision require extraordinary, diverse, lengthy and intimate collaborations among basic scientists, engineers and clinicians. In this review, we present the state of research on a visual neuroprosthesis designed to interface with the occipital visual cortex as a means through which a limited, but useful, visual sense could be restored in profoundly blind individuals. We review the most important physiological principles regarding this neuroprosthetic approach and emphasize the role of neural plasticity in order to achieve desired behavioral outcomes. While full restoration of fine detailed vision with current technology is unlikely in the immediate near future, the discrimination of shapes and the localization of objects should be possible allowing blind subjects to navigate in a unfamiliar environment and perhaps even to read enlarged text. Continued research and development in neuroprosthesis technology will likely result in a substantial improvement in the quality of life of blind and visually impaired individuals.

(Some figures in this article are in colour only in the electronic version)

1. Introduction

Visual impairment is one of the ten most prevalent causes of disability and afflicts millions of people worldwide. Living with acquired blindness not only lowers the quality of life of these individuals, but also strains society's limited resources for assistance, care and rehabilitation. For decades, the possibility of restoring sight to blind individuals has been a subject of intense scientific research [11, 12, 14, 17, 23, 25, 26, 29, 32, 74–76, 89, 90, 103, 106, 114]. Drug development and genetic engineering have had only marginal success in this context, but new hope has been generated by recent advances

in microfabrication technologies, neurosciences, biomaterials, neuromorphic engineering and information technologies leading to the development of highly sophisticated neural prosthetic devices designed to interact with the nervous system [27, 70, 71]. Such assistive devices have already allowed thousands of deaf patients to hear sounds and acquire language abilities [10, 58, 66, 80], and the same hope exists in the field of visual neurorehabilitation. However, the scientific and engineering problems are much more complex than originally believed and there are still many unresolved issues causing a delay in its development.

In this report, we will review some of the principles and problems related to this neuroprosthetic approach and emphasize the role of neural plasticity in order to achieve the desired behavioral outcomes. The role of neuroplasticity has often gone unstated but is key to success in the development of any visual prosthesis.

2. Neural prosthetic interfaces with the nervous system

Neural prosthetics are an emerging technology that use electrical stimulation of the neural tissue to restore function in individuals with disabilities due to damage of the nervous system [40, 59]. Neuroprosthetic devices commonly record and process inputs from outside the body and transmit this information to the nervous system. Examples include cochlear implants for restoring hearing and visual prostheses for restoring vision. A neuroprosthesis, therefore, is a device or a system that communicates with specific groups of neurons to restore as much functionality as possible [97].

The most fundamental requirements of any neural prosthesis are well understood. In order for a device to effectively emulate a neurological system, it has to do three things:

- (1) First, it must collect the same kind of information that the neuronal system normally collects. Consequently, sensory prostheses always include a processing module that mimics the transfer function of biological sensory receptors so that they can be emulated by their artificial counterparts. For example, an auditory prosthesis should be able to capture acoustic signals and a visual prosthesis has to capture the attributes of the visual scene.
- (2) Next, it has to process that information.
- (3) Third, it must communicate the processed information, in an appropriate way, with other parts of the nervous system. Therefore, all neural prostheses need a stable electronic/neural interface that enables selective activation of specific groups of neurons and allow for chronic injection of electrical charge without deterioration of the electrodes or surrounding neural tissue.

As the neural activity evoked by the processing modules is not exactly the same as expected, sensory prostheses must rely on the assumption that the nervous system is able, to a certain degree, adapt to stimuli that differ from what was expected [97].

3. Visual pathways: from real vision to a visual neuroprosthesis

From an engineering point of view, the human visual system consists of two mobile image-acquisition units, the eyes, each with formidable preprocessing circuitry, and a central processing system, located at the occipital part of the brain. Although all parts of the eye are important for perceiving a clear image, the most vital layer for vision is the retina. The retina is essentially a piece of brain tissue that gets direct stimulation from the outside world's lights and images. Visual

input to the retina consists of a stream of photons which can be unequivocally quantified in space and time. The retina performs spatial, temporal and chromatic processing on visual information and converts it into a compact 'digital' format composed of neural impulses [53]. In addition, starting at the retinal level, vision is an active process and eye movements are essential for information processing [39, 112]. Thus, our entire experience of the external visual world derives from the concerted activity of a restricted number of retinal ganglion cells which have to send their information, via the optic nerve, to higher visual centers. The representation has to be unequivocal and fast, in order to ensure object recognition for any single stimulus presentation within a few hundreds of milliseconds [9, 20, 101]. Therefore, the question of how the information about the external world is compressed in the retina and how this compressed representation is encoded in spike trains is an important challenge for the success of any visual prosthesis.

The next processing center is the lateral geniculate nucleus (LGN), which begins to integrate information from both eyes into a binocular representation of visual space. Once retinal signals arrive within the LGN, they are in a position to be influenced by a wide variety of other inputs as well as the complex feedforward and feedback circuits. These inputs include not only visual information that comes from other cortical areas, superior colliculus, pretectum, parabigeminal nucleus and the visual sector of the thalamic reticular nucleus, but also nonvisual information via some of the latter nuclei as well as brain stem pathways [100]. The number of synapses provided by these nonretinal inputs greatly outnumber the number of the parallel pathways coming from the retina, but its function is not fully understood.

The LGN neurons mainly project to the primary visual cortex (also known as the striate cortex or V1), which was the first cortical area clearly identified in the human brain by Gennari in 1782 [42]. Area V1 is located at the back of the head in the occipital lobe and it is here the information is distributed to a number of higher order cortical centers for further processing [41]. It is essential to note, as stated by Hubel and Wiesel, that the primary visual cortex is in no sense the end of the visual pathway [46, 47]. It is just one stage, probably an early one in terms of the degree of abstraction of visual information processing [28, 47, 99, 110].

As blindness can result from an interruption of the normal flow of signals along the visual pathway, a visual prosthesis has to excite the neurons of the pathway at some point after the damaged site [74]. The only requirement is that the device should be in contact with still functioning neural elements. Figure 1 shows the three main approaches for the design of a visual neuroprosthesis (for a review see [55, 64, 75, 89, 103, 106, 114]). Since retinal diseases frequently reduce visual acuity and result in noncurable blindness, several groups worldwide are working on the development of different prosthesis designed to interact with the remaining healthy retina [29, 48, 49, 89, 90, 109, 114, 115] and optic nerve [21, 107, 108]. However the output neurons of the eye, the ganglion cells, often degenerate in many forms of retinal blindness [50, 63], and therefore a retinal or optic nerve

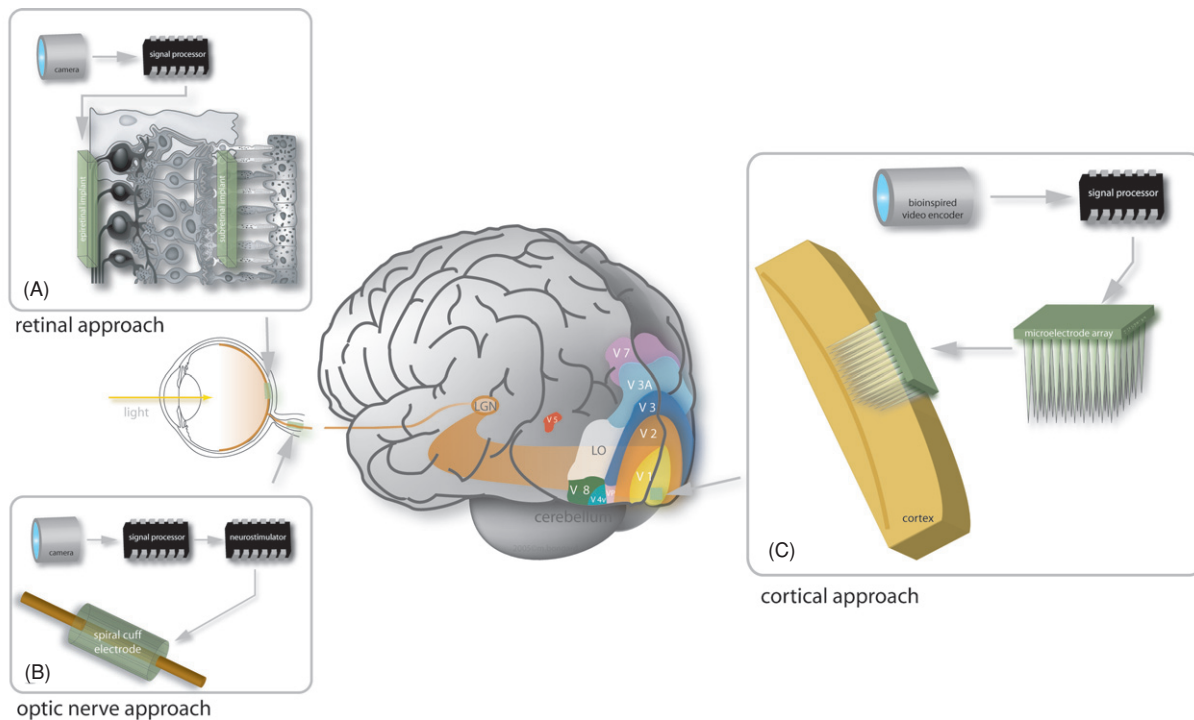


Figure 1. Summary diagram of different approaches to restore vision and the main visual pathways. The inset figures illustrate the approaches in detail. (A) Schematic diagram of a retina cross-section showing two methods of stimulating ganglion cells. The epiretinal device is attached to the inner surface of the retina and stimulates the inner retinal layer based on signals received by a camera and a signal processor. In the subretinal approach, photodiodes are implanted underneath the retina and used to generate currents that stimulate directly the retina. (B) Stimulation of the optic nerve by implanting a cuff electrode around the nerve. (C) Cortical approach. The system uses a bioinspired retina which is able to perform some of the image pre-processing functions of the retina. This bioinspired device transforms the visual world in front of a blind individual into electrical signals that can be used to excite, in real time, the neurons at his/her visual cortex. Although it is not showed, the system includes a way to send power and control signals to implanted electronics.

prosthesis would not be always helpful. This extensive degeneration usually spares the neurons within the higher visual regions of the brain, indicative of the enormous potential of a cortical prosthesis approach [6, 14, 25, 26, 33, 98]. Thus, if these higher visual centers can be stimulated with visual information in a format somewhat similar to the way they were stimulated before the onset of blindness, a blind individual could be able to use this stimulation to extract information about the physical world around him/her [74].

4. Engineering a cortical visual neuroprosthesis

Regardless of the differences in all these approaches, all vision prostheses share a common set of components [64] which are illustrated in figure 2. One or two cameras provide image acquisition, which is then processed by a bioinspired retina-like encoder in order to transform the visual world into electrical signals. This first stage performs a multichannel spatio-temporal filtering to extract and enhance the most relevant features of the scene and also re-encodes this information into a neuromorphic stream of electrode addresses [79]. The second stage serializes the information and transmits it through a radio-frequency link to the implanted device. This RF block provides a wireless transfer of power and data to the internal system [69, 78]. The implanted electronics package

must decode the signals, identify the target electrodes and conform the voltage shape (D/A converter) of the waveform to be applied to the corresponding electrodes located near the target neurons.

The strategy we are employing is not to simply record an image with high resolution, but to transmit information in a meaningful way to the appropriate site(s) in the brain [79]. In order to achieve this, we must take into account the coding features of the biological visual system and design constraints related to the number and distribution of the set of working electrodes the visual scene is mapped to [34, 69, 76]. Figure 3 summarizes the basic architecture of the bioinspired retinal model we are currently using [69, 78, 79]. It is based on information about photoreceptor distribution within human/primate retina and on electrophysiological recordings from populations of retinal ganglion cells. Briefly, the input images are captured by a photosensor array (preferably a logarithmic response camera) and are processed by a set of separate spatial and temporal filters that mimics the function of the photoreceptor, horizontal, amacrine and bipolar cells in order to enhance specific features of the captured visual information. Through a set of parametrized filters and functions, we obtain a portable model that can be easily translated into a hardware description for automatic synthesis using the appropriate tools. The model takes into account the irregular distribution of photoreceptors within the human

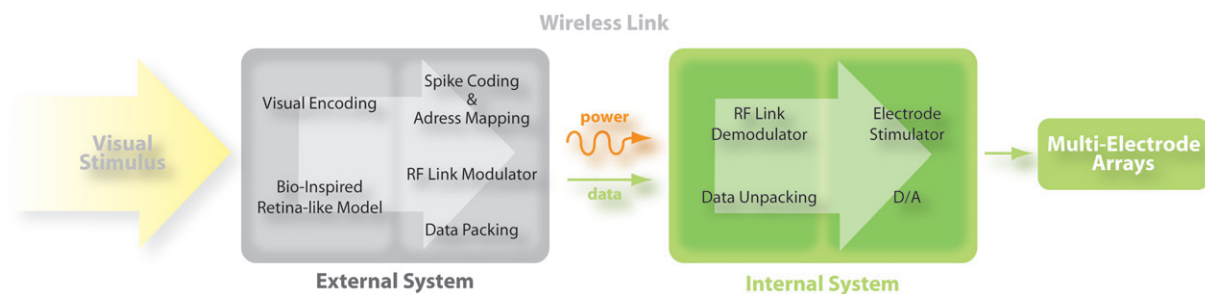


Figure 2. Functional blocks of a visual neuroprosthesis. This includes a bioinspired visual information block (artificial retina) to extract and enhance the most relevant features of the scene. A coding block that translates the retina-like output into pulses modulated with different cadences and temporal lags and whose projection onto the electrode matrix must be fully configurable. An RF block which provides a wireless transfer of power of data and the implanted electronics package which must decode the signals, identify the target electrodes and conform the voltage shape (dc/ac converter) of the final waveforms to be applied to the electrodes located near the target neurons.

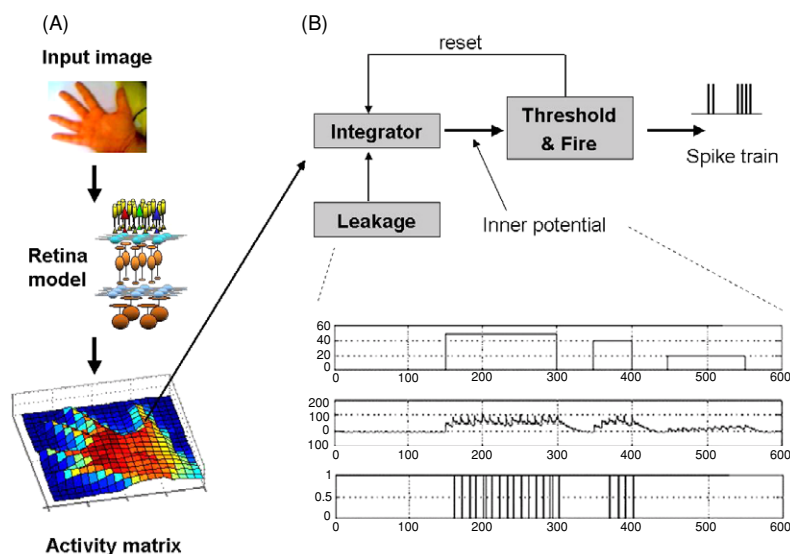


Figure 3. Schematic organization of the bioinspired retinal model. (A) The input images are captured by a photosensor array and processed by a combination of several spatial and temporal filters that enhance specific features of the captured information. The next stage ('activity matrix') reduces the information figure array to the resolution of the electrode matrix, with the option of defining specific receptive field shapes and sizes. (B) Leaky integrate-and-fire spiking neuron model showing the response to a stimulus for a given component of the activity matrix.

retina: a high density of pixels and smaller receptive field sizes in central areas; lower density and bigger receptive fields in peripheral areas. A gain factor can be specified for every individual channel as well as a global gain. The output of these filters is combined to produce an output map we call the 'information figure'. The next stage reduces the information figure array to the resolution of the electrode matrix, with the option of defining specific receptive field shapes and sizes. We refer to this low resolution representation as an 'activity matrix' (figure 3(A)). Finally, mapping and neuromorphic coding (into output pulses that can be sent to each electrode) is carried out and fed through a radiofrequency (RF) link that communicates with the microelectrode array.

The continuously varying components of the activity matrix produced by the retina module are converted into neuromorphic pulse-coded signals through a circuit that emulates the function of retinal ganglion cells (figure 3(B)). The model implemented in the present version of the software

is a simplified version of an integrate-and-fire spiking neuron [37]. Thus, each neuron accumulates input values coming from its receptive field until it reaches a programmable threshold. Then it fires and discharges at the accumulated value. The model also includes a leakage term so that in the absence of a stimulus, the accumulated value will fall to a resting potential. Although the model is essentially analog, we have chosen digital hardware implementation in order to have a more flexible and standardizable approach. In the future, this implementation could be easily customized for each implanted device. Therefore, the implementation of the model in digital hardware provides a flexible design that achieves high performance with response times that are several orders of magnitude lower than that of biological systems. The whole system is presently able to work properly up to 40 MHz. This means that 40 000 electrodes could be stimulated with an inter-spike temporal resolution equal to or lower than 1 ms.

The use of reconfigurable circuitry (FPGA) allows us to adjust and modify the spiking model easily.

The output of the bioinspired retina has to be transmitted to a remote device that electrically connects with the implanted microelectrode array. Ideally, this should be done telemetrically (i.e. without the need of attached wires) to reduce the risk of infection to the patient. Several factors should be taken into account, specially safety, size and power consumption. The full description of the whole system is beyond the scope of this review, but basically it should be able to solve the problem of transmitting data and power to multiple microelectrodes having, simultaneously, the possibility of remote control and sensing of microelectrode status. It implies a compromise between the power level requirements of the stimulation circuits and the signal bandwidth requirements. Our present design has been described elsewhere and incorporates a mixed analog–digital bus which includes stimulus signal, channel selection, digital control signals and power [83]. The system also includes two RF links: a forward link which transmits data from the primary to the secondary system and a backward link which operates in the reverse direction. Both links may operate simultaneously (full-duplex mode) or in half-duplex mode.

It may be argued that emulation of cortical afferents from the lateral geniculate nucleus will provide a more appropriate sensory signal for stimulating primary visual cortex. In particular, it is likely that significant functional transformation of the visual stream occurs at this stage, both as a result of feedforward circuitry as well as the influence (and poorly understood) of cortical–fugal feedback pathway. However, the functional high-order relationships between the outputs of retinal ganglion cells are likely preserved to some extent at the level of the geniculate output [86–88]. A crucial experimental advantage of using a retinally based model is the ability to make multiple simultaneous recordings that allow derivation of firing statistics between ganglion cells, but at present, such technology does not exist for functional (i.e. visually evoked) recordings of the lateral geniculate. This limitation thus necessitates our focus on providing an image of the retinal, as opposed to geniculate, output to the cortical implant.

5. A cortical neuroprosthesis for the blind

The concept of cortically based artificial vision began with studies of the functional architecture of the cerebral cortex. Wilder Penfield and co-workers, during neurosurgical interventions for the treatment of epilepsy, observed that electrical stimulation of the surface of visual cortex induced sensations of light [81, 82]. These percepts, called phosphenes, were usually described as ‘stars in the sky’, ‘clouds’ and ‘pinwheels’, and led a number of investigators to propose that electrical stimulation of visual cortex via arrays of microelectrodes might provide the profoundly blind with a limited form of functional vision. Subsequent experiments by the group of Giles Brindley in England [12–14], William Dobelle at the University of Utah [22, 24–26], Pollen [84] and others [6] showed that stimulation of multiple electrodes simultaneously allowed blind volunteers to recognize simple

patterns, including letters and Braille characters. The results of these studies supported the premise that patterned electrical stimulation of the visual cortex can evoke patterned percepts. However, they also found that a cortical prosthesis based on relatively large electrodes implanted subdurally would have limited usefulness because of factors such as the high levels of current required to produce phosphenes (currents in the range of 1–15 mA, which are deemed unsafe for long-term chronic stimulation), interactions between phosphenes, occasional elicitation of pain due to meningeal or scalp stimulation and risk of inducing epileptic seizures.

Since these early experiments, efforts have been made to develop penetrating multi-electrodes, with exposed tip sizes of the same order of magnitude as the stimulated neurons that can be used to excite neurons more selectively and with electrical currents much smaller than those used by surface stimulation [7, 16, 51, 52, 73, 75, 93, 98, 102, 103]. These new microelectrodes are more closely spaced and therefore may potentially permit higher resolution images, but much is yet to be done in order to achieve an optimal interface with neurons. Important attributes of this interfacing should include:

- Special design for insertion in any part of cerebral cortex, including sulci of highly folded cortices such as those of humans.
- Reaching neurons at the desired three-dimensional location.
- Bi-directional communication with neurons.
- Providing appropriate and stable electrical interfacing with the outside world without significantly disrupting the subject’s physical activity.
- Rendering the devices as inert as possible from the biocompatibility, biostability and biofouling standpoints.
- Minimizing tissue damage and scarring.

A neuroprosthetic system must be implanted into the nervous system and remain fully functional for periods lasting many decades. Therefore, these devices must be highly biocompatible and be able to resist the attack of biological fluids, proteases, macrophages or any substances of the metabolism. Furthermore it is necessary to take into account the possible damage of neural tissues by permanent charge injection using multielectrode arrays. These considerations place unique constraints on the architecture, material and surgical techniques used in the implementation of neural interfaces [75].

One important problem reported with all available microelectrodes to date is long-term viability and biocompatibility. Even those materials generally considered to be biocompatible produce some degree of tissue response. Once implanted, the microelectrodes have to remain within the brain environment for a long time. Although it has been reported that silicon-based shafts, silicon oxide based surfaces and other glass based products are highly biocompatible [94], there are acute and chronic inflammatory reactions which affect both the neural tissue and the surface of the microelectrodes [1, 44, 45, 57, 61, 65, 104, 113]. These reactions often result in damage of neurons and

microelectrodes and lead to the proliferation of a glial scars around the implanted probes which prevents the recording or stimulation of neurons [31, 104].

The inflammatory response is related to the molecular and cellular reactions occurring at foreign surfaces [30, 44]. These responses can be controlled to some degree and some of the main challenges in this field are directed to increasing our understanding of how inflammatory events take place on particular materials and developing new, more biocompatible, surfaces for use in neurosurgery and brain implants. Finally, other possible problems are related with motion stability (i.e. due to the pulsations of the brain) and devices should be fixed so that they remain stable for years. How to keep electrode array biologically and electrically viable remains a difficult problem, and research is underway to propose solutions.

The current level of research may solve many of these problems, but we should be aware that the stimulation patterns needed to evoke visual perception can vary with a number of parameters such as pulse duration, duty cycle, amplitude, number of pulses in a train, etc. Furthermore, these parameters vary for every channel and might take on very different values for each implanted patient. Even for a given subject, these values could change due to electrode encapsulation or neuroplastic changes (see the next paragraph). Moreover, it is necessary to consider other unanswered questions such as:

- What site is most practical for implantation of the device?
- What kind of signals should we send to the brain? With what technology?
- How can we build practical interfaces that exploit available technology?
- How many electrodes are required to produce a useful visual sense?
- How stable are phosphene thresholds and their associated features (i.e. intensity, size, spatial location) on a day-to-day basis?
- Will cortical neurons tolerate long-term electrical stimulation without being altered functionally or morphologically?

A full answer to these questions does not exist. That is, the answers we have so far are incomplete and, in many cases, even conflicting. Further studies with blind subjects as well as more animal models are required to develop optimal stimulation parameters and assess safety and efficacy. In addition, the implantation of several hundred microelectrodes will be essential for determining a blind subject's ability to recognize complex images and evaluate information transfer rates [98]. The current level of research activity may solve these and other related problems, so that these cortical devices could become truly useful and provide a sense of vision to profoundly blind persons however, we should also be sure that the occipital cortex of potential candidates for these neuroprosthetic devices is still capable of processing visual information. The question of what happens with the visual part of the brain when a subject becomes blind is then of seminal importance.

6. Neuroplasticity in blind individuals

In order to interact effectively with their environment, it is obvious that blind individuals have to make striking adjustments to their loss of sight. Perhaps even more astonishing is the fact that these behavioral adaptations are reflected by dramatic neurophysiological changes at the level of the brain. Over the past 25 years, there has been great strides made in understanding the neurophysiological mechanisms underlying visual perception [41]. What is less known is how the brain adapts to the loss of sight. One may pose a very simple question: what is the physiological and functional fate of cortical areas normally associated with the processing of visual information once vision is lost (e.g. from ocular disease or trauma)? With this in mind, what consequences would this have on the success of implementing a cortical-based neuroprosthesis in the hope of restoring functional vision? As research and development continues in the direction of visual neuroprosthetics, it has become increasingly clear that answers to these questions are now becoming crucial [68].

It would seem reasonable to presume that in the setting of visual deprivation, the brain would reorganize itself to exploit the sensory inputs at its disposal and, in fact, the loss of sight has been associated with superior nonvisual perception in the blind, such as auditory and tactile abilities, and even in higher cognitive functions such as grammatical and linguistic processing [8, 85, 92, 105]. There is now growing experimental evidence suggesting that the brain of blind individuals undergoes dramatic changes in response to the loss of sight. These adjustments not only implicate changes in the remaining sensory modalities (for example, touch and hearing) but also involve those parts of the brain once dedicated to the task of vision itself. Specifically, it appears that the occipital visual cortex, normally associated with the processing of visual information, is recruited in a functional and compensatory manner to process the remaining sensory modalities [4, 15, 38, 43, 60]. Figure 4 shows an example. It displays the areas of the occipital cortex that are activated when a sighted person views a black-white checkerboard reversing at 8 Hz (figure 4(A)) and the corresponding areas activated when an early blind subject reads Braille characters (figure 4(B)) [35]. As we can see, there is a marked activation and overlap of the occipital part of the brain in both cases.

The functional significance of this cross-modal plasticity by which the occipital, formerly visual cortex is recruited for processing of tactile information is supported by a variety of additional, converging data [15, 95, 96]. In both congenitally and late-blind individuals, it has been shown that parts of the occipital cortex are activated during tactile tasks such as Braille reading. Furthermore, this activation is not epiphenomenal but actually functionally significant as supported by the fact that reversible disruption of occipital cortex function (for example by transcranial magnetic stimulation (TMS)) impairs Braille reading ability in the blind [19]. A clinical report also lends supports the notion that the processing occurring within occipital cortical areas is essential for tactile processing. Following a bilateral occipital stroke, a congenitally blind patient, once highly Braille proficient, lost the ability to

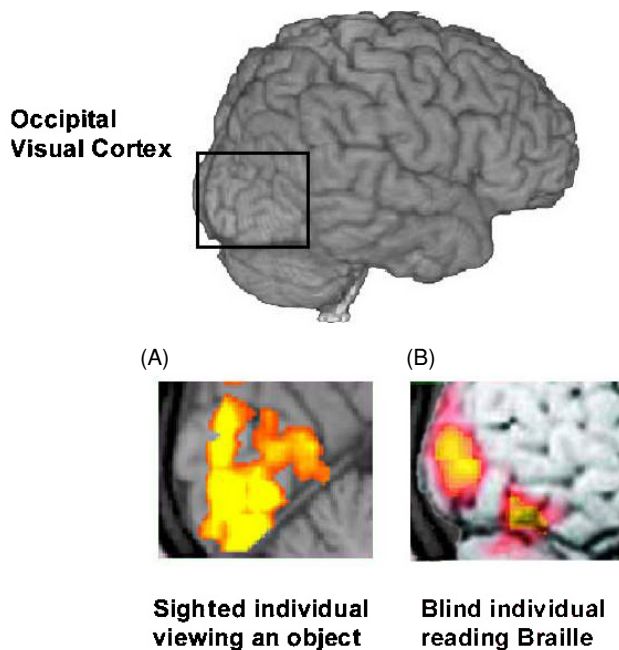


Figure 4. Functional magnetic resonance imaging (fMRI) study showing the areas of the occipital cortex that are activated when a sighted subject views a black-white checkerboard reversing at 8 Hz (A), and when an early blind subject reads Braille characters using a fMRI compatible Braille stimulator (B). In both cases, there is a marked activation of the occipital cortex, illustrating that the occipital parts of the brain utilized by sighted subjects to process visual information are transformed in some blind subjects and utilized to process tactile information.

read Braille [43]. Although she could discriminate everyday objects by touch, she also showed striking deficits in tasks requiring fine spatial discriminations [67].

In parallel, increasing evidence has also demonstrated that the occipital cortex is recruited for the processing of auditory information. Activation of occipital cortical areas has also been demonstrated in congenitally blind subjects during tasks of auditory localization [54, 111]. This issue was further addressed by assessing language-related brain activity implicated in speech processing and auditory verb-generation. It has been shown that speech comprehension activates not only parts of the brain associated with language (as with sighted adult controls) [91], but also striate and extra-striate regions of the visual cortex [4]. As with tactile processing, reversible functional disruption of the occipital cortex by TMS impairs verb-general performance only in blind subjects [3] providing further evidence that the recruitment of the occipital cortex in high-level cognitive processing is functionally relevant.

However, some blind or severely visually deprived subjects do not adapt well to the loss of sight. In these subjects, preliminary studies suggest that the occipital cortex is not or at most, only partially reorganized [33]. This appears to be particularly the case in severely visually impaired but not absolute blind subjects. Similarly, late blind subjects are more likely to fall into this category. Such subjects never fully adapt to the world of touch and sound. For them, a

neuroprosthetic approach by which implanted electrodes into the occipital cortex are used for induction of visual percepts might be a functionally desirable solution.

Other important questions are related to the temporal course of the plastic changes and whether cortical areas deprived of their normal sensory input can still process the lost sensory modality. In this context, we have recently reported a late blind patient (with no light perception in the latest 12 years), who suddenly experienced elementary and complex visual hallucinations located in his right visual field [2]. The only pathological feature in this subject was an arteriovenous malformation located in his left striate cortex. Although the underlying pathophysiology of visual hallucinations in this patient is uncertain, these hallucinations could represent an increased level of excitability following an abnormal cortical release phenomenon [18, 62] or the result of an ‘irritative’ phenomenon reflecting the pathological activation of neural ensembles in the regions where the occipital lesion is located [5]. Pathophysiology notwithstanding, these findings provide evidence that the occipital cortex of some blind subjects is still able to process visual information and strengthen the notion that long-term deafferented occipital cortex can remain functionally active and be potentially recruited to process visual information despite the complete absence of visual input. Thus, a precise understanding of the time-course and mechanisms of the adaptive changes after sensory deprivation will be crucial in developing and projecting the success of novel visual neuroprosthetic approaches.

7. Lessons learned from other neuroprostheses efforts

In terms of restoring lost sensory function, cochlear implant research has arguably been the most successful and has translated into a viable therapeutic option for some profoundly deaf patients [10, 58, 66, 80]. Simply explained, a wire electrode bundle is surgically inserted into the inner ear thus serving as an electronic replacement for damaged hair cells. A microphone and speech processor picks up and decodes sounds from the environment and the coded signals drive in turn the electrodes that stimulate the nerve fibers of the cochlea processing sound waves and creating the sensation of hearing. In conjunction with intense rehabilitation programs that are tailored to the individual, deaf individuals can learn to comprehend and in some cases, even acquire speech. By analogy, immediately after the microelectrodes are implanted in the occipital cortex, the expected phosphenes are likely to engender a poor perception of any object. However after some time and adequate training, the reorganization and cognitive abilities of the highly adaptive neuronal networks of the brain will result in improved performance and more concordant perceptions. Furthermore, the patterns of stimulation are likely to change over time due to factors such as the progression of disease, changes in electrode stimulation thresholds and the effects of learning and plasticity thus creating new associations between the patterns of electrical stimulation and the visual patterns perceived (figure 5).

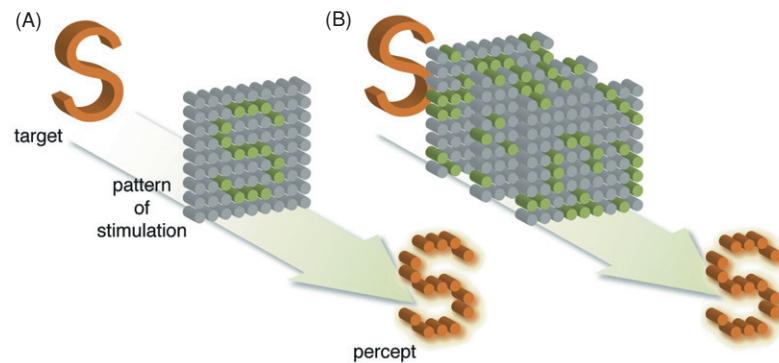


Figure 5. Proposed relation between patterns of electrical stimulation, neural activity and visual percepts. (A) Based on the known physiology of retinotopic projections, it was initially proposed that a given electrical pattern of stimulation generated on the surface of the retina, optic nerve or visual cortex, would be expected to generate a visual percept of the same pattern. (B) Current notions incorporate recent evidence that the relation between the pattern of stimulation and visual percept is nonlinear and nonconformal. Furthermore, the patterns of stimulation are likely to change over time due to such factors as the progression of retinal disease, changes in electrode stimulation thresholds, and the effects of learning and plasticity as an individual learns to create new associations between the patterns of electrical stimulation and the visual patterns perceived (inspired by [74]).

Evidence from research investigating neuroplasticity in the deaf and following cochlear implantation bears striking parallels with the case seen in visual neuroprostheses development. For example, similar to activation of the occipital cortex by auditory stimuli in the blind, the auditory cortex (Brodmann's areas 41, 42 and 22) is activated in deaf subjects in response to visual stimuli [36] including the observation of sign-language [72]. Thus, as in the case of the blind, the removal of one sensory modality leads to neural reorganization of the remaining ones. Visual-auditory plasticity in the deaf has also been found in patients with cochlear implants. Neuroimaging studies indicate that after implantation of a cochlear device, primary auditory cortex is activated by the sound of spoken words in deaf patients who had lost hearing before the development of language. Interestingly, the levels of baseline activity before implantation were positively correlated with the extent of language improvement following the operation. It appears that if metabolism in the auditory cortex is restored by cross-modal plasticity changes before implantation, the auditory cortex no longer responds to signals from a cochlear implant and patients do not show improvement in language capabilities [56]. These results have important implications and may even have parallel implications with respect to neuroplastic changes following blindness. It is important to note that not all neuroplastic changes following sensory loss might be beneficial or lead to functional recovery. Neuroplasticity can contribute to changes that are functionally adaptive when a sensory modality is lost but it can also limit the degree of adaptation [77]. The lesson to be learned is that simple re-introduction of the lost sensory input by itself might not be sufficient to restore the lost sense. Specific strategies are necessary to modulate information processing by the brain and to extract relevant and functionally meaningful information from neuroprosthetic inputs.

8. Challenges and future perspectives

The development and realization of neuroprosthetic devices requires extraordinary, diverse, lengthy and intimate collaborations among basic scientists, engineers and clinicians. If we can understand more about the fundamental mechanism of neuronal coding, and how to safely stimulate the nervous system, there will be real potential in applying this knowledge clinically. However, we should be aware that there are still a number of important unanswered questions and that many problems have to be solved before a visual neuroprosthesis can be considered a viable clinical therapy or option.

Several studies have highlighted that following the loss of vision, the brain undergoes profound neuroplastic transformation and that the occipital cortex is a major site of these changes. The extent and magnitude of these neuroplastic changes is likely to be influenced by such factors as the cause, onset and duration of blindness. The precise understanding of these neuroplastic processes will be crucial in developing and projecting the success of novel, visual neuroprosthetic strategies, which has implications for rehabilitative training and device development.

In light of the evidence of cross-modal plasticity occurring within the visual cortex following blindness, two questions can be raised in regard to stimulating implants aimed at restoring functional vision. First, it might be argued that an individual may actually be hindered by a cortical stimulating implant. It is possible that once the occipital cortex is recruited to carry out tasks in other sensory modalities, artificial stimulation may disrupt proper processing of tactile and auditory information [8]. For example, it has been shown that occipital cortical stimulation in early-blind proficient Braille readers (using TMS) can give rise to erroneous and even phantom tactile sensations [19]. Thus, fitting these subjects with cortical visual prostheses might lead to tactile, or synaesthetically joined tactile and visual percepts rather than meaningful and interpretable vision and even more importantly, potentially

disrupt tactile and auditory performance crucial to a blind individual's own daily functioning. Secondly, cross-modal plasticity might negatively affect any attempt to restore visual function (by way of decreased visual cortical excitability and therefore rendering the visual cortex less responsive to visual stimulation). It remains to be determined how visual and tactile/auditory 'inputs' would interact in a multimodal visual cortex.

Despite very encouraging pioneering efforts in developing a functional visual prosthesis, these questions have yet to be addressed. Given the importance of all these issues in the dynamic recruitment of the visual cortex, clearly the choice and viability of any neural prosthesis should take these factors into consideration in the hope of restoring any degree of functional vision in the blind.

We propose that in restoring functional vision in the blind, one must first understand how the brain adapts to blindness and uncover adaptive resources such as cross-modal representations. One possibility might be to envision a patient-controlled system that coordinates and registers the visual perceptions generated by a visual prosthesis with the identification of objects perceived through other senses (such as touch and audition). Patients could learn to integrate these concordant sources of sensory stimuli into meaningful percepts and, ultimately, allow them to identify objects in the visual world [68].

Success in restoring functional vision depends on our understanding of how blindness affects the brain and what it means to 'see' again. The neural changes that result from loss of vision need to be addressed if the restoration of visual input is to lead to functional vision. These issues of neuroplasticity also lead to questions regarding the feasibility of a visual prosthesis approach and its potential benefit to blind individuals. Therefore, it is essential that future research explore the mechanisms that underlie brain plasticity following the loss of vision. Such insight could help develop and refine strategies for merging visual sensations that are generated by the prosthesis, which are then perceived by the patient, with sensory information obtained by other modalities.

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